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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 63/04, C07D 307/77, A61K 31/19 — A2

(11) International Publication Number: WO 98/42650

(43) International Publication Date: 1 October 1998 (01.10.98)

(21) International Application Number: PCT/US98/05455

(22) International Filing Date: 19 March 1998 (19.03.98)

(30) Priority Data:
60/040,870 21 March 1997 (21.03.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING CYSTIC FIBROSIS

(57) Abstract

This invention provides methods for the treatment or inhibiting of the symptoms of cystic fibrosis which comprises administering to a mammal in need thereof an effective amount of a compound having activity as a leukotriene B_4 antagonist.

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LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inherited disease that usually manifests itself in early childhood. Increasing numbers of children with cystic fibrosis are now surviving into young adulthood: the median age of survival currently exceeds 30 years. Some patients have a variant form of the disease in which symptoms first appear during adolescence or adulthood.

More than 200 different cystic fibrosis transmembrane conduct and regulator (CFTR) mutations have been detected. Although the function of CFTR remains unknown, it appears to be closely involved with chloride transport across epithelial membranes.

Nearly all exocrine glands are affected in the pathology of CF in varying distribution and degree of severity. Involved glands fall into 3 types: (1) those that become obstructed by viscid or solid eosinophilic material in the lumen (pancreas, intestinal glands, intrahepatic bile ducts, gallbladder, submaxillary glands); (2) those that produce an excess of histologically normal secretions (tracheobronchial and Brunner's glands); and (3) those that are normal histologically but secrete excessive Na and Cl (sweat, parotid, and small salivary glands). Duodenal secretions are viscid and contain an abnormal mucopolysaccharide.

It is likely that impaired tracheobronchial clearance of the abnormal secretions leads to widespread mucous plugging of airways with secondary bacterial infection and consequent generalized bronchiectasis. The bacterial flora in the airways is highly stereotyped: early in the course of the disease, *S.aureus* is found in the sputum; subsequently, mucoid strains of *P.aeruginosa* are isolated

(mucoid in this context refers to a slimy substance secreted by the colony of organisms growing on a culture plate).

Fifty percent of all patients present with pulmonary manifestations usually consisting of chronic cough and wheezing associated with recurrent or chronic pulmonary infections. Cough is the most troublesome complaint, often accompanied by gagging, vomiting, and disturbed sleep. With disease progression, there are intercostal retractions, use of accessory muscles of respiration, a barrel-chest deformity, digital clubbing, and cyanosis. Upper respiratory tract involvement includes nasal polyposis and opacification of the paranasal sinuses. Teenagers may have retarded growth, delayed onset of puberty, and a declining tolerance for exercise. Pulmonary complications in adolescents and adults include pneumothorax, hemoptysis, and right heart failure secondary to pulmonary hypertension. Insulin-requiring diabetes develops in 2 to 3% of patients, and multinodular biliary cirrhosis with varices and portal hypertension develops in 4 to 5% of adolescents and adults. Chronic and/or recurrent abdominal pain may be related to intussusception, peptic ulcer disease, periappendiceal abscess, pancreatitis, gastroesophageal reflux, esophagitis, gallbladder disease, or episodes of partial intestinal obstruction secondary to abnormally viscid fecal contents.

The chest radiograph may strongly suggest the diagnosis of cystic fibrosis. Extrapulmonary manifestations may also suggest the diagnosis of cystic fibrosis. Prominent among these findings are pancreatic insufficiency with consequent steatorrhea, recurrent partial intestinal obstruction caused by abnormal fecal accumulation (so-called meconium ileus equivalent), heat prostration, hepatic cirrhosis, and aspermia in males.

A sweat test with pilocarpine iontophoresis performed in an experienced laboratory is highly sensitive and specific for cystic fibrosis. Sweat chloride concentrations exceeding 60 mEq/L are found in 98 percent of patients with cystic fibrosis. Although sweat chloride concentrations

increase with age, values greater than 80 mEq/L are not found in normal persons or in patients with any other respiratory illness.

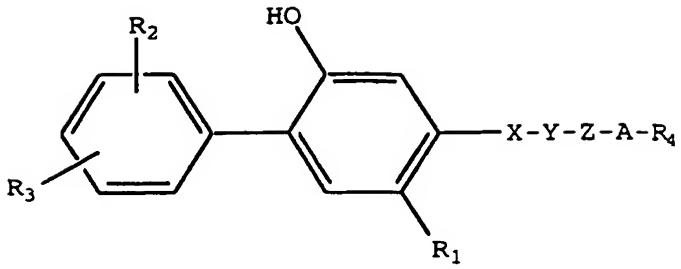
Treatment of cystic fibrosis includes management of infections and use of respiratory therapy modalities designed to mobilize secretions, including regular percussion and postural drainage.

Research in the area of allergic reactions of the lung has provided evidence that arachidonic acid derivatives formed by the action of lipoxygenases are related to various disease states. Some of these arachidonic acid metabolites have been classified as members of a family of eicosatetraenoic acids termed leukotrienes. Three of these substances are currently thought to be major components of what has been previously called slow reacting substance of anaphylaxis (SRS-A) and have been designated leukotrienes C_4, D_4, and E_4 (LTC_4, LTD_4, and LTE_4, respectively).

Another arachidonic acid metabolite, leukotriene B_4 (LTB_4), is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, asthma, inflammatory bowel diseases, and other inflammatory states characterized by the infiltration and activation of polymorphonuclear leukocytes and other proinflammatory cells. Thus activated, the polymorphonuclear leukocytes liberate tissue-degrading enzymes and reactive chemicals causing the inflammation. Antagonism of LTB_4 should therefore provide a novel therapeutic approach to treatment of these and other LTB_4 mediated conditions.

Because of the debilitating effects of cystic fibrosis there continues to exist a need for effective treatment.

This invention provides a method for the treatment or inhibiting cystic fibrosis in mammals comprising administering to a mammal in need thereof an effective amount of a compound of Formula I



I

wherein:

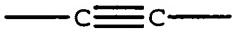
R_1 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2 and R_3 are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-$S(O)_q$-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X is -O-, -S-, -C(=O), or $-CH_2-$;

Y is -O- or $-CH_2-$;

or when taken together, -X-Y- is -CH=CH- or

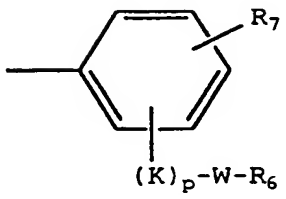


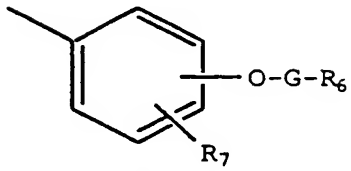
;

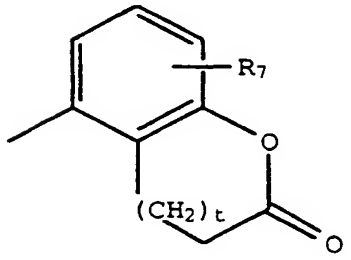
Z is a straight or branched chain C_1-C_{10} alkylidenyl;

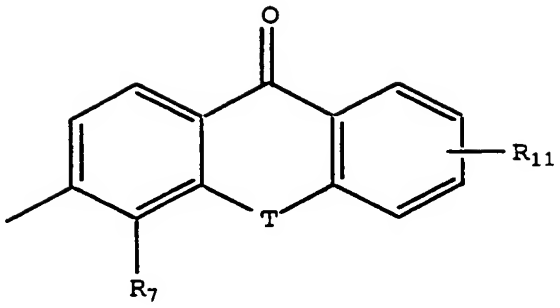
A is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

R_4 is R_6









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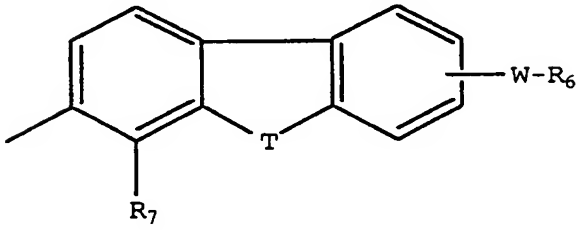

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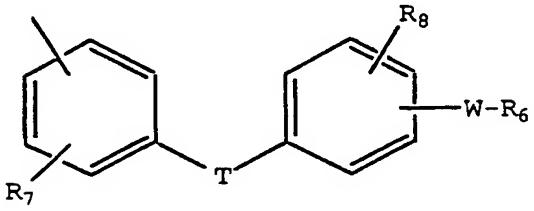


where,

each R_6 is independently -COOH, 5-tetrazolyl, -CON(R_9)$_2$, or -CONHSO$_2$$R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, -W-R_6, -T-G-R_6, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, -W-R_6, or -T-G-R_6;

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $-S(O)_q-$;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

provided when A is -O- or -S-, R_4 is not R_6;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

provided W is not a bond when p is 0;

or a pharmaceutically acceptable salt or solvate thereof.

The following definitions refer to the various terms used throughout this disclosure.

The term "C_1-C_5 alkyl" refers to the straight and branched aliphatic radicals of 1 to 5 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, and the like. Included within this definition are the terms "C_1-C_3 alkyl" and "C_1-C_4 alkyl".

The term "C_2-C_5 alkenyl" refers to straight and branched aliphatic radicals of 2 to 5 carbon atoms containing one double bond, such as $-CH=CH_2$, $-CH_2CH=CH_2$, $-CH_2CH_2CH=CH_2$, $-CH_2C(CH_3)=CH_2$, $-CH_2CH=C(CH_3)_2$, and the like.

The term "C_2-C_5 alkynyl" refers to straight and branched aliphatic residues of 2 to 5 carbon atoms containing one triple bond, such as $-C\equiv CH$, $-CH_2-C\equiv CH$, $-CH_2CH_2C\equiv CH$, $-CH_2CH(CH_3)C\equiv CH$, $-CH_2C\equiv CCH_3$, and the like.

The term "C_1-C_4 alkoxy" refers to methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, and tert-butoxy.

The term "halo" refers to fluoro, chloro, bromo, and iodo.

The term "C_1-C_{10} alkylidenyl" refers to a divalent radical derived from a C_1-C_{10} alkane such as $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH(CH_3)-$, $-CH_2C(CH_3)_2-$, $-CH_2CH(C_2H_5)-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(C_2H_5)CH_2-$, $-CH_2CH_2CH(C_2H_5)-$, $-C(CH_3)_2CH_2CH_2-$, $-CH(CH_3)CH_2CH(CH_3)-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2CH_2CH(C_2H_5)CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-(CH_2)_{10}-$, and the like. Included within this definition are the terms "C_1-C_4 alkylidene" and "C_2-C_4 alkylidene".

The term "C_4-C_8 cycloalkyl" refers to a cycloalkyl ring of four to eight carbon atoms, such as cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dimethylcyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "straight or branched chain divalent hydrocarbyl residue of one to eight carbon atoms" refers to a divalent radical derived from a straight or branched alkane, alkene, or alkyne of one to eight carbon atoms. Depending upon the branching and number of carbon atoms, as will be appreciated by organic chemists, such a moiety can contain one, two or three double or triple bonds, or combinations of both. As such, this term can be considered an alkylidene group as defined above containing from 1 to 8 carbon atoms optionally containing one to three double or triple bonds, or combinations of the two, limited as noted in the preceding sentence.

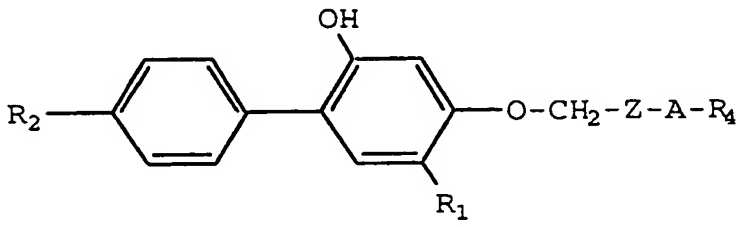
This invention includes the pharmaceutically acceptable base addition salts of the compounds of Formula I. Such salts include those derived from inorganic bases, such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines, such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkylamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methyl amine, diethyl amine, ethylene diamine, cyclohexylamine, ethanolamine, and the like. The potassium and sodium salt forms are particularly preferred.

This invention includes both mono-salt forms, i.e., a 1:1 ratio of a compound of Formula I with a base as previously described, as well as di-salt forms in those instances where a compound of Formula I has two acidic groups. In addition, this invention includes any solvate forms of the compounds of Formula I or salts thereof, such as ethanol solvates, hydrates, and the like.

It is recognized that in compounds having branched alkyl, alkylidenyl, or hydrocarbyl functionality, and in those compounds bearing double or triple bonds, various stereoisomeric products may exist. This invention is not limited to any particular stereoisomer but includes all

possible individual isomers and mixtures thereof. The term "5-tetrazolyl" refers to both tautomers, ie, (1H)-5-tetrazolyl and (2H)-5-tetrazolyl.

A most preferred group of compounds employed in the methods of the present invention are those compounds of Formula Ia:



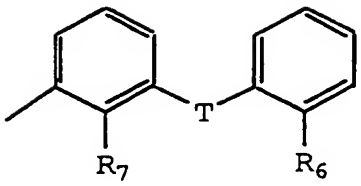
Ia

and pharmaceutically acceptable base addition salts thereof. Especially preferred are those compounds wherein R_2 is halo, particularly fluoro. Preferred R_1 substituents are propyl and especially ethyl.

Preferred Z substituents include C_2-C_4 alkylidene, particularly $-CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2-$. Preferred A groups include -O-, $-CH_2-$, -CH(R_7-substituted phenyl)-, and $-C(CH_3)_2-$.

Preferred R_4 groups include -COOH, 5-tetrazolyl, or a mono-, di-, or tri-cyclic group as drawn above wherein there is at least one acidic group attached to a ring, such as -W-COOH, -T-G-COOH, or the corresponding tetrazole derivatives. The preferred W moiety is that of a bond or straight chain C_1-C_4 alkylidene; preferred G moieties are straight chain C_1-C_4 alkylidene. It is preferred that R_5 or R_7 be C_1-C_4 alkyl, especially n-propyl.

Particularly preferred groups are those wherein A is -CH(R_7-substituted phenyl)- and R_4 is -COOH or 5-tetrazolyl. Also preferred are those compounds wherein A is -O- and R_4 is



Preferred aspects of this substructure are those wherein R_7 is C_1-C_4 alkyl, especially n-propyl, and R_6 is -W-COOH. Particularly preferred are those compounds wherein T is -O- or -S- and W is a bond.

Particularly preferred compounds of the instant invention include 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid; 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid; 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane ; 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid; 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

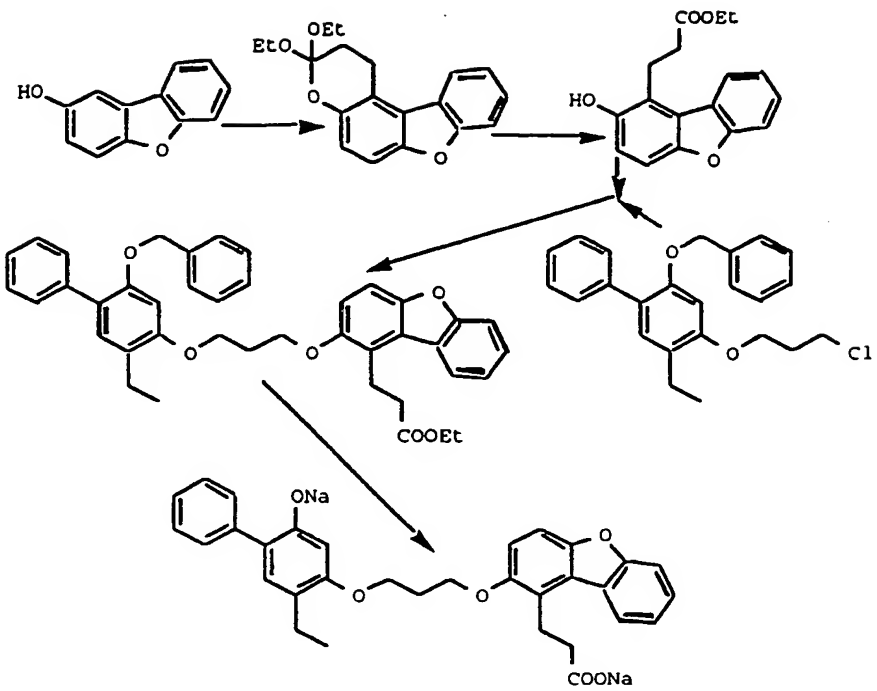
The leukotriene B_4 (LTB_4) antagonists employed in the methods of the present invention may be synthesized essentially as described in US Patent No. 5,462,954 issued October 31, 1995, the entire contents of which are herein incorporated by reference.

The following examples further illustrate the preparation of the intermediates and compounds employed in this invention. The examples are illustrative only and are not intended to limit the scope of the invention. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. All chemical shifts are reported in parts per million (_) relative to tetramethylsilane. Chemical shifts

of aromatic protons of quinoline species in DMSO-d_6 are concentration dependent. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined on a CEC-21-110 spectrometer using electron impact (EI) conditions, a MAT-731 spectrometer using free desorption (FD) conditions, or a VG ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. Silica gel chromatography was performed using ethyl acetate/hexane gradients unless otherwise indicated. Reverse-phase chromatography was performed on MCI CHP20P gel using an acetonitrile/water or methanol/water gradient unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted. Where structures were confirmed by infra-red, proton nuclear magnetic resonance, or mass spectral analysis, the compound is so designated by "IR", "NMR", or "MS", respectively.

Example 1

3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt



A. Preparation of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran.

A solution of 2-hydroxydibenzofuran (5.00 g, 27.2 mmol), triethylorthoacrylate (10.1 g, 54.3 mmol) and pivalic acid (1.39 g, 13.6 mmol) in toluene (100 mL) was refluxed for 18 hours. The mixture was cooled to room temperature and washed once with water and once with a saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide an orange oil. This material was diluted with hexane and maintained at -20°C for 18 hours. The resulting crystals were collected via vacuum filtration to provide 5.67 g (67%) of the desired title intermediate, mp 64°C; NMR ($CDCl_3$) 7.96 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.35 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 3.82 (q, J = 7.2 Hz, 2H), 3.73 (q, J = 6.8 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.0 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); MS-FD m/e 312

(p); IR ($CHCl_3$, cm^{-1}) 2982, 1494, 1476, 1451, 1434, 1251, 1090, 1054, 975.

Analysis for $C_{19}H_{20}O_4$:

Calc: C, 73.06; H, 6.45;

Found: C, 72.81; H, 6.72.

B. Preparation of 3-[1-(2-hydroxydibenzofuran)]-propanoic acid ethyl ester.

A mixture of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran (3.50 g, 11.2 mmol) and 10% aqueous hydrochloric acid (5 mL) in ethyl acetate (30 mL) was stirred at room temperature for 1 hour. The resulting mixture was washed once with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide a tan solid. Recrystallization from hexane/ethyl acetate provided 3.11 g (98%) of the desired title intermediate as an off-white crystalline material: mp 128-131°C; NMR ($CDCl_3$) 7.88 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.36 (t, J = 6.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.13 (q, J = 8.8 Hz, 2H), 3.43 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 7.7 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); MS-FD m/e 284 (100, p), 256 (65), 238 (17); IR (KBr, cm^{-1}) 2985 (b), 1701, 1430, 1226, 1183, 1080.

Analysis for $C_{17}H_{16}O_4$:

Calc: C, 71.82; H, 5.67;

Found: C, 71.90; H, 5.43.

C. Preparation of 3-[2-[3-[[5-ethyl-2-(phenylmethoxy)-[1,1'-biphenyl]-4-yl]oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester.

3-[1-(2-Hydroxydibenzofuran)]propanoic acid ethyl ester (625 mg, 2.20 mmol) was dissolved in dimethylformamide (10 mL) and carefully treated at room temperature with 95% sodium hydride (58 mg, 2.4 mmol). When gas evolution had

ceased, 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (836 mg, 2.20 mmol) was added and the resulting mixture was stirred for 18 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a dark oil. Silica gel chromatography (ethyl acetate/hexane) provided 200 mg (14%) of the desired titled intermediate as a colorless oil: NMR ($CDCl_3$) 8.11 (d, J = 7.7 Hz, 1H), 7.57 (m, 3H), 7.48 (t, J = 7.3 Hz, 1H), 7.20-7.44 (m, 10 H), 7.17 (s, 1H), 7.08 (d, J = 8.9 Hz, 1H), 6.67 (s, 1H), 5.05 (s, 2H), 4.29 (t, J = 6.2 Hz, 2H), 4.26 (t, J = 6.1 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 8.5 Hz, 2H), 2.67 (m, 4H), 2.37 (t, J = 6.0 Hz, 2H), 1.21 (m, 6H).

D. Preparation of 3-[2-[3-[(5-ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt.

To a nitrogen-purged solution of 3-[2-[3-[[5-ethyl-2-(phenylmethoxy)[1,1'-biphenyl]-4-yl]oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester (200 mg, 0.318 mmol) in a 1:1 mixture of methanol/tetrahydrofuran (40 mL) was added 10% palladium on carbon (25 mg). The resulting suspension was hydrogenated at 1 atm pressure for 24 hours at room temperature. The mixture was filtered through a short pad of Florisil® and the filtrate concentrated *in vacuo*. The residue was dissolved in a 1:1 mixture of methanol/tetrahydrofuran (20 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 24 hours. The resulting mixture was extracted once with diethyl ether. The aqueous layer was acidified with 5N hydrochloric acid solution and extracted twice with methylene chloride. The combined methylene chloride fractions were concentrated *in vacuo*. The residue was dissolved in a minimum of 1N sodium hydroxide solution and purified on HP-20 resin to provide 53 mg (30%) of the desired title product as a fluffy white

solid: NMR (DMSO-d_6) 8.12 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.37-7.57 (m, 5H), 7.30 (m, 2H), 7.14 (m, 2H), 6.96 (s, 1H), 6.93 (s, 1H), 4.30 (t, J = 7.3 Hz, 2H), 4.14 (t, J = 5.4 Hz, 2H), 2.48 (m, 4H), 2.23 (m, 4H), 1.10 (t, J = 7.6 Hz, 3H); MS-FAB m/e 555 (88, p + 1), 533 (62); IR ($CHCl_3$, cm^{-1}) 3384 (b), 2969, 1566, 1428, 1257, 1181.

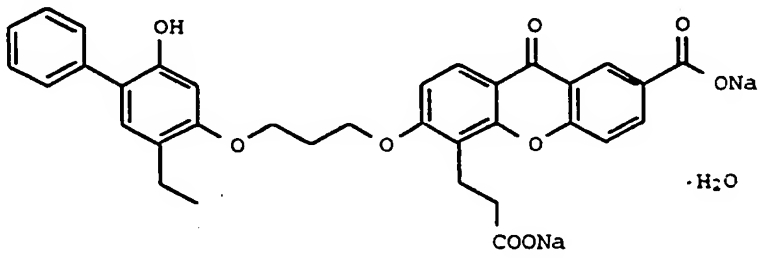
Analysis for $C_{32}H_{28}O_6Na_2$:

Calc: C, 69.31; H, 5.09;

Found: C, 69.51; H, 5.39.

Example 2

7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate



A mixture of 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (749 mg, 1.97 mmol), ethyl 7-carboethoxy-3-hydroxy-9-oxo-9H-xanthene-4-propanoate (729 mg, 1.97 mmol), potassium carbonate (1.36 g, 9.85 mmol) and potassium iodide (33 mg, 0.20 mmol) was refluxed for 24 hours. Dimethylsulfoxide (2 mL) was added and heating continued for 24 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed once with water. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to reveal a tan solid. This material was dissolved in ethyl acetate (30 mL) and the resulting solution purged with nitrogen. To this solution was added 10% palladium on carbon (120 mg) and the

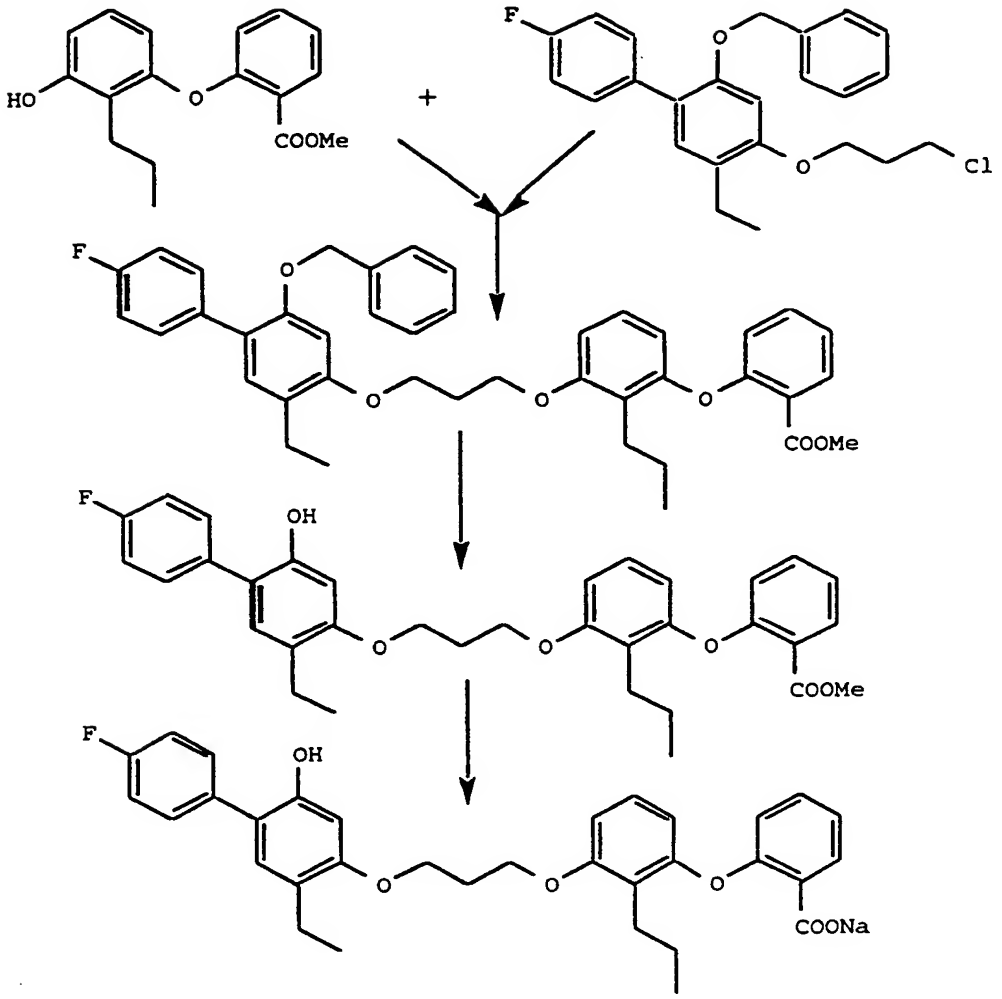
resulting suspension hydrogenated at 1 atmosphere of pressure. The solution was filtered and concentrated *in vacuo* to provide a colorless oil. This material was dissolved in a solution of 1:1 methanol/tetrahydrofuran (30 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 18 hours. The resulting solution was extracted once with diethyl ether and the aqueous layer acidified with 5N hydrochloric acid solution. The resulting precipitate was collected via suction filtration. This material was converted to the di-sodium salt and purified as described above for the preparation of Example 1(D) to provide 390 mg (56%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 12.65 (s, 1H, -OH), 8.65 (s, 1H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.50 (m, 3H), 7.29 (t, J = 7.8 Hz, 2H), 7.17 (m, 2H), 6.93 (s, 1H), 6.89 (s, 1H), 4.26 (m, 4H), 3.12 (m, 2H), 2.47 (m, 2H), 2.23 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); MS-FAB m/e 627 (24, p), 605 (40), 583 (24), 331 (24), 309 (100); IR (KBr, cm^{-1}) 3419 (b), 2962, 1612, 1558, 1443, 1390, 1277, 1084.

Analysis for $C_{34}H_{28}O_9Na_2 \cdot H_2O$:

Calc: C, 63.34; H, 4.69;
Found: C, 63.36; H, 4.50.

Example 3

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt



A. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-benzoic acid methyl ester.

A mixture of 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene (20.0 g, 50.2 mmol) and sodium iodide (75.3 g, 502 mmol) in 2-butanone (200 mL) was refluxed for 6 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a colorless oil. This material was dissolved in

dimethylformamide (100 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (14.4 g, 50.2 mmol) and potassium carbonate (20.8 g, 151 mmol) at room temperature for 24 hours. This mixture was diluted with water and twice extracted with ether. The aqueous layer was separated and back-extracted once with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. Silica gel chromatography provided 25.4 g (78%) of the desired title intermediate as a pale golden oil: NMR ($CDCl_3$) 7.91 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.25-7.43 (m, 6H), 7.03-7.38 (m, 5H), 6.84 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 4.24 (t, J = 5.7 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.69 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.34 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 5.0 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); MS-FD m/e 648 (p); IR ($CHCl_3$, cm^{-1}) 2960, 1740, 1604, 1497, 1461, 1112.

Analysis for $C_{41}H_{41}O_6F$:

Calc:	C, 75.91; H, 6.37;
Found:	C, 76.15; H, 6.45.

B. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (33.0 g, 50.9 mmol) was de-benzylated as described above for the preparation of Example 2 to provide 27.3 g (96%) of the title intermediate as an amber oil: NMR ($CDCl_3$) 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.42 (m, 3H), 7.05-7.23 (m, 4H), 6.99 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 6.46 (d, J = 8.1 Hz, 1H),

5.05 (s, 1H, -OH), 4.23 (m, 4H), 3.86 (s, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.36 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); MS-FD m/e 558 (p); IR ($CHCl_3$, cm^{-1}) 2965, 1727, 1603, 1496, 1458, 1306, 1112.

Analysis for $C_{34}H_{35}O_6F$:

Calc:	C, 73.10; H, 6.31;
Found:	C, 73.17; H, 6.42.

C. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester (21.5 g, 38.5 mmol) was hydrolyzed as described above for the preparation of Example 2. The acid was converted to the sodium salt and purified as described above for the preparation of Example 1(D) to provide 16.7 g (77%) of the desired title product as a white amorphous solid: NMR (DMSO-d_6) 10.50 (bs, 1H, -OH), 7.51 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (m, 2H), 7.00 (m, 2H), 6.95 (s, 1H), 6.67 (dd, J = 8.2, 3.3 Hz, 2H), 6.62 (s, 1H), 6.26 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 2.16 (t, J = 5.9 Hz, 2H), 1.45 (hextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS-FAB m/e 568 (38, p + 1), 567 (100, p), 544 (86), 527 (77), 295 (65), 253 (45); IR (KBr, cm^{-1}) 3407 (b), 2962, 1603, 1502, 1446, 1395, 1239, 1112.

Analysis for $C_{33}H_{32}O_6FNa$:

Calc:	C, 69.95; H, 5.69; F, 3.35;
Found:	C, 69.97; H, 5.99; F, 3.52.

The methods of the present invention describe the use of leukotriene antagonists for the treatment or

inhibition of cystic fibrosis which is characterized by the excessive release of leukotriene B_4.

The term "excessive release" of a leukotriene refers to an amount of the leukotriene sufficient to exacerbate the symptoms of cystic fibrosis. The amount of leukotriene which is considered to be excessive will depend on a variety of factors, including the amount of leukotriene required to cause the symptoms of disease, and the species of the mammal involved. As will be appreciated by those skilled in the art, the success of treating a mammal suffering from cystic fibrosis characterized by an excessive release of leukotriene with a compound of Formula I will be measured by the regression or prevention of the symptoms of the condition.

Cystic fibrosis is a multi-organ disease arising from an abnormality of the chloride ion channel that regulates transportation of chloride ions across fluid-transporting epithelial cells. The defect leads to altered secretions, blocked ducts and reduced mucosal defenses to infections. Ultimately, patients become hosts for chronic, recurring infections such as *Pseudomonas aeruginosa* in the lung. Once the infection persists in this organ, a chronic inflammatory response ensues with massive infiltration of neutrophils. The sputum becomes extremely viscous due to accumulation of DNA from degraded neutrophils. In addition, much of the tissue damage in the lung is a result of proteases and reactive oxidants released by these granulocytes.

Assays

Assay 1

The effectiveness of compounds of Formula I to inhibit the binding of tritiated LTB_4 to guinea pig lung membranes was determined as follows.

[^{3}H]-LTB_4 Radioligand Binding Assay in Guinea Pig Lung Membranes

[^{3}H]-LTB_4 (196-200 Ci/mmole) was purchased from New England Nuclear (Boston, MA). All other materials were purchased from Sigma (St. Louis, MO). Incubations (555 mL) were performed in polypropylene minitubes for 45 minutes at 30°C and contained 25 mg of guinea pig lung membrane protein (Silbaugh, et al., European Journal of Pharmacology, 223 (1992) 57-64) in a buffer containing 25 mM MOPS, 10 mM $MgCl_2$, 10 mM $CaCl_2$, pH 6.5, approximately 140 pM [^{3}H]-LTB_4, and displacing ligand or vehicle (0.1% DMSO in 1 mM sodium carbonate, final concentration) as appropriate. The binding reaction was terminated by the addition of 1 mL ice cold wash buffer (25 mM Tris-HCl, pH 7.5) followed immediately by vacuum filtration over Whatman GF/C glass fiber filters using a Brandel (Gaithersburg, MD) 48 place harvester. The filters were washed three times with 1 mL of wash buffer. Retained radioactivity was determined by liquid scintillation counting at 50% counting efficiency using Ready Protein Plus cocktail (Beckman, Fullerton, CA). Nondisplaceable binding was determined in the presence of 1 mM LTB_4 and was usually less than 10% of total binding. Data were analyzed using linear regression analysis of log-logit plots of the values between 10% and 90% of control binding to calculate IC_{50}s and slope factors (pseudo-Hill coefficients). IC_{50} values thus obtained were corrected for radioligand concentration (Cheng and Prusoff, Biochem. Pharmacol., 22, 3099 (1973)) to calculate K_i values. pKi is the mean -log K_i for n experiments.

Compounds of the instant invention tested in the above assay were found to have a pKi of between 7 and 11.

A chronic endobronchial infection in rats serves as a good model of the inflammatory response associated with cystic fibrosis (Konstan, et al., Am. Rev. Respir. Dis., 141, 186-92, 1990).

Assay 2

For an inoculum, a slurry of agarose beads containing 10^7 colony-forming units per ml of *P.aeruginosa*, strain 3064 (a mucoid isolate from a cystic fibrosis patient) is prepared. Young adult male rats weighing 150 grams are lightly anesthetized with ether and inoculated in the left lung with 60 µl of the slurry using a bead-tipped 20 gauge needle inserted through a tracheal incision. Control groups are injected with sterile untreated beads. Animals are housed in hanging cages and allowed free access to rat chow and water. Oral dosing with a compound of formula I or vehicle is done twice daily for a period of 14 days. Daily weights of each animal are recorded.

At the end of the dosing period, the rats are sacrificed by exsanquination. Lungs from half of the animals in each treatment group are used to make histological examinations; lungs from the other half are used for quantitative bacteriologic counts. The lungs used for histologic examination are initially fixed in 10% formalin in phosphate-buffered saline (PBS). The left lungs are then cut sagitally into 3 slices, 3 mm thick, and the entire medial, central and lateral surfaces embedded in paraffin, then sectioned at 5 µm thickness and stained with hematoxylin-eosin. For comparison with non-infected tissue, a midsagittal slice of the right lung is also similarly processed. Stained sections are viewed at 160-fold magnification. Each section is divided into units of 0.75

mm square size and each square scored for the presence or absence of inflammation. Inflammatory foci consist of inflammatory cells as well as areas of necrosis and fibrosis. Six hundred squares are counted in the left lung and 300 in the right lung. For bacteriologic examination, lungs are removed aseptically and homogenized in 50 ml of PBS. Serial dilutions are spread on replicate tryptic soy agar plates and colony-forming units counted after 20 hours incubation at 37°C. Dose-response effects are obtained by dividing the animals into 4 experimental groups of 20 rats each. Animals in these groups are treated with either vehicle, or 10, 25 or 50 mg/kg doses of a compound of formula I. The effectiveness of a treatment is mainly assessed by comparing the percentage of left lung involved in inflammation of the treated group to that of the vehicle control. Comparisons of weight gain and lung bacteriologic counts between the groups serve as secondary parameters of interest.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit or treat the symptoms of cystic fibrosis.

The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining and slowing, stopping or reversing progression, severity or a resultant symptom. As such, the present method includes both medical therapeutic and/or prophylactic administration as appropriate.

While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the present invention. The compounds or

formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 0.01 to 90% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Such formulations are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the formulations employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable carriers, excipients and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, water, syrup, and methyl cellulose.

The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compounds of this invention may be delivered transdermally using known transdermal delivery systems and excipients. Most preferably, a compound of this invention is admixed with permeation enhancers including, but not limited to, propylene glycol, polyethylene glycol monolaurate, and azacycloalkan-2-ones, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers, and buffers may be added to the transdermal formulation as desired.

For topical administration, a compound of this invention ideally can be admixed with any variety of excipients in order to form a viscous liquid or cream-like preparation.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention include capsules, tablets and aerosols.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof that is

effective to inhibit or treat the symptoms of cystic fibrosis.

Advantageously for this purpose, formulations may be provided in unit dosage form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the route of administration the age, weight and response of the individual patient, the condition being treated and the severity of the patient's symptoms.

In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any serious side effects and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

While all of the compounds illustrated above exemplify LTB_4 inhibition activity in vitro, we have also discovered that compounds bearing a single acidic group (R_6) are considerably more orally bioactive when administered to mammals compared with those compounds bearing two such

acidic groups. Thus, a preferred embodiment when administering compounds of Formula I orally to mammals comprises administering compounds bearing a single acidic R_6 functionality.

The following formulation examples may employ as active compounds any of the compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propanoic acid	250
Starch	200
Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Magnesium stearate	5

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight %
3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid	0.25
Ethanol	30.00
Propellant 11 (trichlorofluoromethane)	10.25
Propellant 12 (Dichlorodifluoromethane)	29.75
Propellant 114 (Dichlorotetrafluoroethane)	29.75

The active compound is dissolved in the ethanol and the solution is added to the propellant 11, cooled to -30°C. and transferred to a filling device. The required amount is then fed to a container and further filled with the pre-mixed propellants 12 and 114 by means of the cold-filled method or pressure-filled method. The valve units are then fitted to the container.

Formulation 4

Tablets each containing 60 mg of active ingredient are made up as follows:

2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid sodium salt	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60° and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-phenyl]-4-pentynoic acid	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient are made as follows:

3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propanoic acid	250
Starch	200
Magnesium stearate	10

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	50 mg
Sodium carboxymethyl cellulose	50 mg
Sugar	1 g
Methyl paraben	0.05 mg
Propyl paraben	0.03 mg
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose, sugar, and a portion of the water to form a suspension. The parabens, flavor and color are dissolved and diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

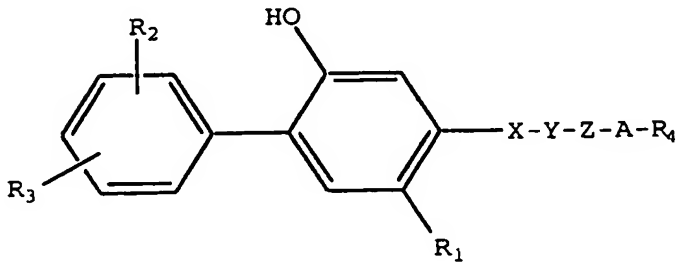
An intravenous formulation may be prepared as follows:

2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy] benzoic acid	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

We claim:

1. A method for treating or inhibiting cystic fibrosis in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of the formula I



I

wherein:

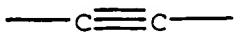
R_1 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2 and R_3 are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-S(O)q-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X is -O-, -S-, -C(=O), or $-CH_2-$;

Y is -O- or $-CH_2-$;

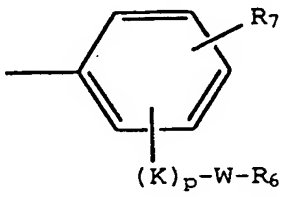
or when taken together, -X-Y- is -CH=CH- or

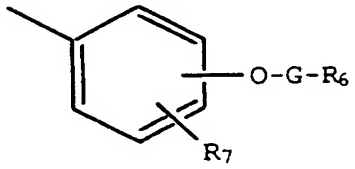

;

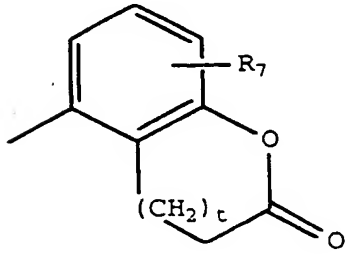
Z is a straight or branched chain C_1-C_{10} alkylidenyl;

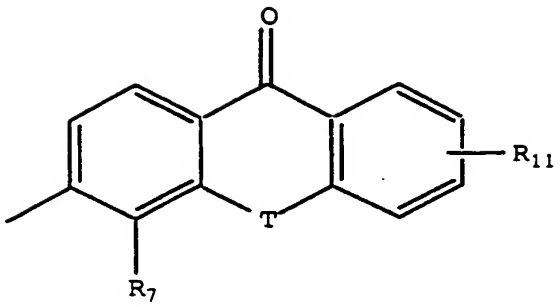
A is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

R_4 is R_6 ,









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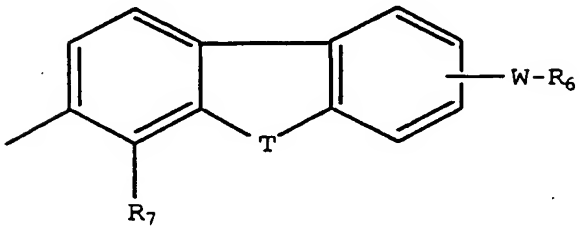

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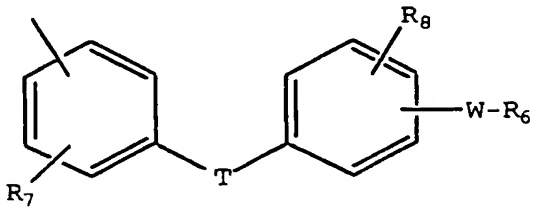


where,

each R_6 is independently -COOH, 5-tetrazolyl, -CON(R_9)$_2$, or -CONHSO$_2$$R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, -W-R_6, -T-G-R_6, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, -W-R_6, or -T-G-R_6;

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $-S(O)_q-$;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

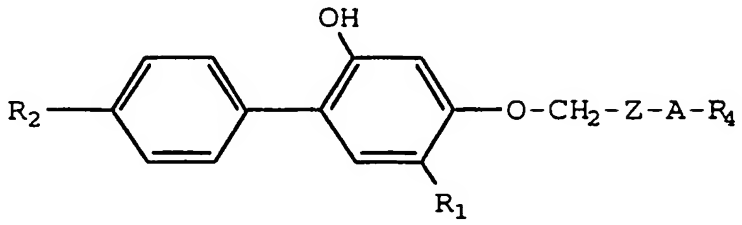
provided when A is -O- or -S-, R_4 is not R_6;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

provided W is not a bond when p is 0;

or a pharmaceutically acceptable salt or solvate thereof.

2. The method as claimed in **Claim 1** employing a compound of the formula



or a pharmaceutically acceptable salt or solvate thereof.

3. The method as claimed in **Claim 2** employing 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable salt or solvate thereof.

4. The method as claimed in **Claim 2** employing 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid or a pharmaceutically acceptable salt or solvate thereof.

5. The method as claimed in **Claim 2** employing 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane or a pharmaceutically acceptable salt or solvate thereof.

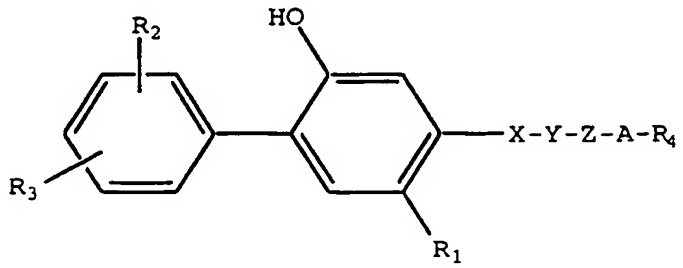
6. The method as claimed in **Claim 2** employing 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid or a pharmaceutically acceptable salt or solvate thereof.

7. The method as claimed in **Claim 2** employing 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-

hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

8. The method as claimed in any one of **Claims 1 to 7** in which the mammal is a human.

9. Use of a compound of formula I



I

wherein:

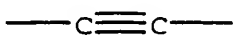
R_1 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2 and R_3 are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-$S(O)_q$-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X is -O-, -S-, -C(=O), or $-CH_2-$;

Y is -O- or $-CH_2-$;

or when taken together, -X-Y- is -CH=CH- or

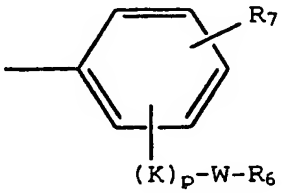


;

Z is a straight or branched chain C_1-C_{10} alkylidenyl;

A is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

R_4 is R_6 ,



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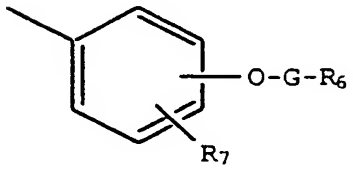

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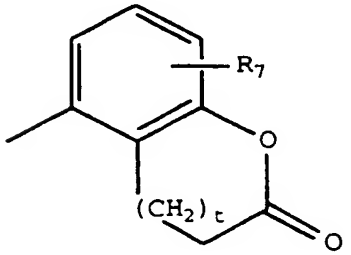

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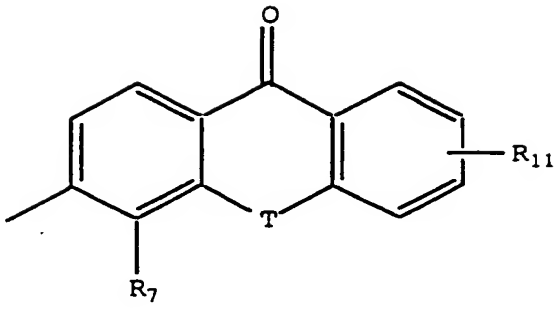

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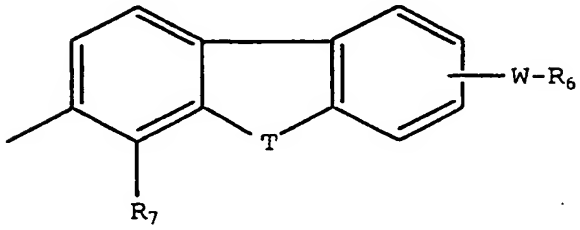

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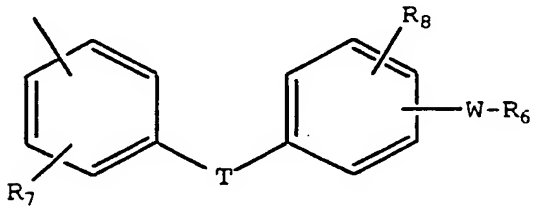


where,

each R_6 is independently -COOH, 5-tetrazolyl, -CON(R_9)$_2$, or -CONHSO$_2$$R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, -W-R_6, -T-G-R_6, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, -W-R_6, or -T-G-R_6;

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $-S(O)_q-$;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

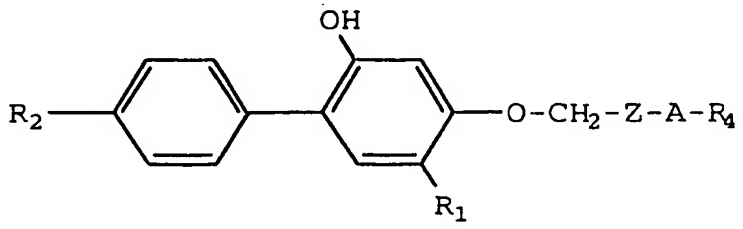
provided when A is -O- or -S-, R_4 is not R_6;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

provided W is not a bond when p is 0;

or a pharmaceutically acceptable salt or solvate thereof, optionally in combination with a pharmaceutically acceptable excipient, for the preparation of a pharmaceutical composition for the treatment or inhibiting of cystic fibrosis in a mammal.

10. The use according to **claim 9** employing a compound of the formula;



or a pharmaceutically acceptable salt or solvate thereof.

11. The use according to **claim 9** wherein the compound employed is 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable salt or solvate thereof.

12. The use according to **claim 9** wherein the compound employed is 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid or a pharmaceutically acceptable salt or solvate thereof.

13. The use according to **claim 9** wherein the compound employed is 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane or a pharmaceutically acceptable salt or solvate thereof.

14. The use according to **claim 9** wherein the compound employed is 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid or a pharmaceutically acceptable salt or solvate thereof.

15. The use according to **claim 9** wherein the compound employed is 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 63/04, C07D 307/77, A61K 31/19 — A3

(11) International Publication Number: WO 98/42650

(43) International Publication Date: 1 October 1998 (01.10.98)

(21) International Application Number: PCT/US98/05455

(22) International Filing Date: 19 March 1998 (19.03.98)

(30) Priority Data:
60/040,870 21 March 1997 (21.03.97) US

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(74) Agents: LENTZ, Nelsen, L. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
23 December 1998 (23.12.98)

(54) Title: LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING CYSTIC FIBROSIS

(57) Abstract

This invention provides methods for the treatment or inhibiting of the symptoms of cystic fibrosis which comprises administering to a mammal in need thereof an effective amount of a compound having activity as a leukotriene B_4 antagonist.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05455

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 63/04; C07D 307/77; A61K 31/19
US CL :549/385, 391; 560/56; 514/453, 455, 568, 569, 571

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/385, 391; 560/56; 514/453, 455, 568, 569, 571

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,552,441 A (DILLARD et al.) 03 September 1996, entire document	1-15
X	US 5,563,164 A (CLEMENS et al.) 08 October 1996, entire document.	1-15
X	US 5,462,954 A (BAKER et al.) 31 October 1995, entire document	1-15
X	US 5,478,857 A (CLEMENS et al.) 26 December 1995, entire document.	1-15
X	US 5,543,428 A (SAWYER et al.) 06 August 1996, entire document.	1-15

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Date of the actual completion of the international search

11 SEPTEMBER 1998

Date of mailing of the international search report

17 SEP 1998

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